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(57) Abstract

The present invention relates to the use of ridogrel for the manufacture of a medicament for treating inflammatory bowel diseases, wherein ridogrel is administered in a daily dose from 0.01 mg/kg body weight to 0.5 mg/kg body weight; pharmaceutical compositions comprising ridogrel.

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LOW DOSE RIDOGREL FORMULATIONS AND THEIR USE FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASES

The present invention relates to the use of ridogrel at low dosages in the treatment of inflammatory bowel diseases and to corresponding low dose ridogrel formulations.

EP-0,221,601 describes (E)-5-[[[(3-pyridinyl)[3-(trifluoromethyl)phenyl] methylene]amino]oxy]pentanoic acid (generically known as ridogrel) for use in various pathological conditions. This document also generically discloses pharmaceutical compositions comprising ridogrel.
EP-0,448,274 describes a tablet formulation comprising 400 mg of ridogrel for use in ulcerative and inflammatory conditions of the gastrointestinal tract.
Casellas et al., 1992, Gastroenterology 102 (4, Suppl.), p. A601, and Casellas et al., 1993, Gastroenterology 104 (4, Suppl.), p. A677 describe the clinical effect of the administration of ridogrel, 300 mg b.i.d., in ulcerative colitis.

The use of ridogrel in the treatment of inflammatory bowel diseases as described in the prior-art shows limited clinical efficacy and displays undesired side-effects. The use as described in claim 1 solves this problem by administering ridogrel at low doses, thereby unexpectedly increasing the clinical efficacy in inflammatory bowel diseases and reducing adverse side-effects.

Ridogrel as defined herein refers to (E)-5-[[[(3-pyridinyl)[3-(trifluoromethyl) phenyl]methylene]amino]oxy]pentanoic acid and can be prepared in accordance with the procedures described in EP-0,221,601. Ridogrel can also be used according to this invention as a pharmaceutically acceptable acid or base addition salt thereof. When a pharmaceutically acceptable acid or base addition salt is used, the dose referred to hereinabove and hereinunder is based upon the amount of ridogrel as such.

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the acid addition salt forms which can conveniently be obtained by treating the base form of the compounds of formula (I) with appropriate acids such as inorganic acids, for example, hydrohalic acid, e.g. hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like acids; or organic acids, such as, for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric,

malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids. Preferred acids to form acid addition salts are hydrochloric acid, which forms a (1:1) salt with ridogrel and nitric acid, which also forms a (1:1) salt with ridogrel.

Conversely, said acid addition salt forms can be converted in the free base forms by treatment with an appropriate base. The compounds of formula (I) which are acidic may form base addition salt forms. The pharmaceutically acceptable base addition salts as mentioned hereinabove are meant to comprise the base addition salts forms which can conveniently be obtained by treating the acid form of the compounds of formula (I) with appropriate bases. Examples of such salts may include lithium, sodium, potassium, calcium, aluminium, gold and silver salts. Also contemplated are salts with pharmaceutically acceptable amines such as ammonia, primary, secondary and tertiary amines, such as alkyl amines, hydroxyalkylamines, N-methylglucamine and the like. Conversely, said base addition salt forms can be converted in the free acid forms by treatment with an appropriate acid.

Preferred counter ions in a base addition salt form are lithium and sodium.

The present invention relates to the use of ridogrel or a pharmaceutically acceptable acid or base addition salt thereof for the manufacture of a medicament for treating inflammatory bowel diseases, wherein ridogrel or its pharmaceutically acceptable acid or base addition salt form is administered in a daily dose from 0.01 mg/kg body weight to 1 mg/kg body weight, suitably to 0.5 mg/kg body weight (the dose based upon the amount of ridogrel present as such).

Alternatively, the invention relates to a method of treating humans suffering from inflammatory bowel diseases, said method comprising the administration to said humans of ridogrel or a pharmaceutically acceptable acid or base addition salt form thereof in an amount from 0.01 mg/kg body weight to 1 mg/kg body weight, suitably to 0.5 mg/kg body weight.

In particular, ridogrel or a pharmaceutically acceptable acid or base addition salt form thereof is used in a daily dose from 0.02 mg/kg body weight to 0.1 mg/kg body weight, more particularly in a dose of about 0.05 mg/kg body weight.

For adult human beings, the above cited dose ranges in mg/kg body weight correspond to a dose range from about 1 mg/day to about 50 mg/day, in particular from about 2 mg/day to 10 mg/day, more in particular of about 5 mg/day.

Inflammatory bowel diseases include, for example, ulcerative colitis, Crohn's disease and the like. In particular, ridogrel is used in the treatment of ulcerative colitis. Ulcerative colitis is characterized by the presence of lesions in the mucous membranes of the colon. It is generally believed that thromboxane plays an active role in the development of these lesions. Ridogrel has been described to show both thromboxane synthetase inhibitory activity and thromboxane receptor antagonistic activity. Unexpectedly, it has been shown that at the doses of the present invention, however, ridogrel is a mere thromboxane synthetase inhibitor, lacking thromboxane receptor antagonistic activity.

The treatment of inflammatory bowel diseases includes both the treatment of the acute disease state, thereby inducing remission of the disease or improvement of the lesions or clinical condition, as well as the use in maintenance therapy. A satisfactory treatment of inflammatory bowel diseases, in particular ulcerative colitis, is characterized by a good clinical efficacy and a low occurrence of adverse events. In particular, after 8 weeks of treatment, the following findings are desirable:

- an endoscopic improvement in more than 45% of the patients, preferably in more than 50% of the patients;
- a complete endoscopic cure in more than 10% of the patients, preferably in more than 30% of the patients;
- a median percentage of days with bloody stools during the last 2 weeks of treatment of below 50%, preferably below 10%;
- a percentage of patients wherein the investigator's global evaluation of the effect of the treatment is good or excellent of more than 40%, preferably more than 60%; and
- an occurrence of adverse events in less than 40% of the patients. Adverse events that may occur are e.g. nausea, vomiting, diarrhoea, abdominal cramps, oedema, paraesthesia, hematoma, ecchymoses, and the like.

Ridogrel or its pharmaceutically acceptable acid or base addition salt form is suitably administered systemically, such as orally, rectally, intraperitoneally or parenterally. Preferably, ridogrel is administered orally or rectally. Suitably, ridogrel or a pharmaceutically acceptable acid or base addition salt form thereof is administered once daily (o.d.) or twice daily (b.i.d.), preferably formulated in an appropriate pharmaceutical composition. Hence, the invention relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and ridogrel or its pharmaceutically acceptable acid or base addition salt form in an amount effective to be used as defined hereinabove. In particular, the invention relates to a pharmaceutical

composition comprising from 0.5 to 5 mg ridogrel per dosage unit form and a pharmaceutically acceptable carrier.

Solid pharmaceutical compositions such as tablets, capsules, suppositories and the like, suitably comprise ridogrel in an amount from 0.5 to 5 mg per dosage unit form, in particular from 1 to 5 mg per dosage unit form. In solid pharmaceutical compositions the active ingredient is preferably ridogrel as such. Liquid pharmaceutical compositions such as oral solutions, oral suspensions, oral syrups, injectable solutions, rectal enema's or rectal solutions, rectal foams and the like, suitably comprise ridogrel in an amount from 0.1 to 1 mg/ml, preferably from 0.5 to 1 mg/ml. In liquid pharmaceutical compositions ridogrel is preferably present as the sodium salt of the ridogrel.

Dosage unit form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of ridogrel. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of ridogrel is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration.

Solid compositions according to the present invention will preferably comprise pharmaceutically acceptable carriers and excipients, such as fillers e.g. lactose, sucrose, mannitol, maize starch, microcrystalline cellulose or calcium hydrogen phosphate; lubricants e.g. stearic acid, polyethylene glycol, magnesium stearate, talc or silica; disintegrants e.g. rice, potato or maize starch, sodium starch glycolate or croscarmellose sodium ; binding agents e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl-methylcellulose and wetting agents e.g. sodium dioctylsulfosuccinate and Polysorbates. Interesting solid compositions comprise by weight based on the total weight of the composition from 60% to 90% fillers, from 3% to 10% disintegrants and from 0.5% to 5% binding agents. For the preparation of solid compositions according to the invention, ridogrel is blended with suitable excipients and granulated. Preferably, ridogrel is granulated with the filler or fillers before admixture of the other excipients. Most preferably the fillers employed will be lactose monohydrate and maize starch, especiallly in combination with calcium hydrogen phosphate. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form.

Liquid compositions may comprise any of the usual pharmaceutical media such as water, glycols, oils, alcohols and the like. Interesting liquid compositions are aqueous solutions or suspensions, in particular for rectal administration. Liquid oral compositions may comprise, apart from ridogrel or a pharmaceutically acceptable acid or preferably base addition salt form and water, flavouring substances; sweeteners; suspending agents, e.g. cellulose derivatives; wetting agents, e.g. polyoxyethylene derivatives of sorbitan esters; buffer systems; stabilizing agents; preservatives; solubility enhancers and the like. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed.

For rectal administration, conventional compositions such as suppositories or enemas may be used. Preferably, rectal solutions may be used. Said rectal solutions comprise apart from the active ingredient ridogrel or its pharmaceutically acceptable acid or preferably base addition salt, water (suitably demineralised, preferably free of pyrogenics), a suitable buffer, such as the combination of disodium hydrogen phosphate and sodium dihydrogen phosphate, a thickening and stabilising agent such as for example hydroxyethyl cellulose, and an agent to make the solution isotonic, such as sodium chloride.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. Particular pharmaceutical compositions are controlled release formulations, from which the active ingredient is gradually released after administration.

It may be advantageous that a micronized form of ridogrel is used in the present compositions. These micronized forms may be prepared by micronization techniques known in the art, e.g. by milling in appropriate mills and sieving through appropriate sieves.

Optionally, ridogrel may be administered in combination with another agent effective in the treatment of inflammatory bowel diseases, e.g. sulphasalazine, mesalazine, olsalazine, balsalazide, a corticosteroid and the like. The combined use includes the simultaneous, separate or sequential administration of the therapeutic agents.

In a further aspect, the invention relates to a product containing (a) ridogrel and (b) sulphasalazine, mesalazine or a corticosteroid, as a combined preparation for simultaneous, separate or sequential use in the treatment of inflammatory bowel diseases.

Experimental part

Pharmaceutical compositions

1. 1 mg oral tablet

Tablets having the composition shown hereinunder were prepared according to art-known formulation procedure.

Ridogrel	1 mg	1.00 %
Calcium hydrogen phosphate dihydrate	0.94 mg	0.94 %
Lactose monohydrate	56.01 mg	56.01 %
Maize starch	24 mg	24.00 %
Croscarmellose sodium(1)	2 mg	2.00 %
Sodium lauryl sulphate	0.25 mg	0.25 %
Hypromellose 2910 15 mPa.s(2)	2 mg	2.00 %
Microcrystalline cellulose	10 mg	10.00 %
Croscarmellose sodium[1]	3 mg	3.00%
Colloidal anhydrous silica	0.3 mg	0.30 %
Magnesium stearate	0.5 mg	0.50 %

(1) Croscarmellose sodium is the British Approved Name of sodium carboxymethyllcellulose.

(2) Hypromellose 2910 15 mPa.s is the British Approved Name for methylhydroxypropylcellulose, the four digit number (2910) is an indication of the substitution on cellulose, i.e. the first two digits represent the approximate percentage composition of methoxyl groups, and the third and fourth digits the approximate percentage composition of hydroxypropyl groups. The grade used in this example is indicated by the viscosity of a 2 % solution at 20°C, i.e. 15 mPa.s

2. 5 mg oral tablet

Tablets having the composition shown hereinunder were prepared according to art-known formulation procedure.

Ridogrel	5 mg	5.00 % (w/w)
Calcium hydrogen phosphate dihydrate	4.7 mg	4.70 % (w/w)
Lactose monohydrate	48.25 mg	48.25 % (w/w)
Maize starch	24 mg	24.00 % (w/w)
Croscarmellose sodium[1]	2 mg	2.00% (w/w)
Sodium lauryl sulphate	0.25 mg	0.25 % (w/w)
Hypromellose 2910 15 mPa.s[2]	2 mg	2.00 % (w/w)
Microcrystalline cellulose	10 mg	10.00 % (w/w)
Croscarmellose sodium[1]	3 mg	3.00 % (w/w)
Colloidal anhydrous silica	0.3 mg	0.30 % (w/w)
Magnesium stearate	0.5 mg	0.50 % (w/w)

The percentages are based on the total weight of the tablet.

3. Oral solution 0.25 mg/ml

The rectal solution of 1 litre having the composition as shown hereinunder were prepared as follows (the amounts shown hereinunder are given for the preparation of 1 ml of rectal solution) :

800 ml of demineralised water was basified by adding approximately 1.6 ml of a aqueous sodium hydroxide solution (0.1 N). Said solution was heated to a temperature ranging from 60 to 70 °C. The 6.5 g hydroxy ethylcellulose was added to the solution while stirring vigorously. Said mixture is stirred for about 10 minutes at the above-mentioned temperature after which the heating is stopped. The stirring is continued until the hydroxy ethylcellulose is dissolved completely. Subsequently 250 mg ridogrel is added to the solution as well as 2.085 g disodium hydrogen phosphate anhydrous and 477 mg of sodium dihydrogen phosphate. Furthermore the 3.5 g of sodium chloride are added and 200 ml of deminieralised water is added.

The pH of the final solution should range between about 6.5 and 8.5, preferably the pH should be between 7.2 and 7.6.

The solutions are packaged in enema bottles containing 40 ml or 80 ml of the above described solution.

It is important use the correct amount and grade of hydroxy ethyl cellulose in view of stability of the obtained solutions.

Composition :		
Ridogrel	0.25 mg	0.025 %
Hydroxy ethylcellulose (4800-6000 mPa.s)	6.5 mg	0.65 %
Disodium Hydrogen Phosphate anhydrous	2.085 mg	0.285 %
Sodium Dihydrogen Phosphate Monohydrate germ poor	0.477 mg	0.0477 %
Sodium Hydroxide	q.s to dissolve the Ridogrel	
Sodium Chloride	3.5 mg	0.35 %
Purified water qs ad	1000 µl	q.s. ad 100 %

Analogous solutions containing 2.5 mg to 10 mg of ridogrel in 40 ml of rectal solution or 2.5 mg to 10 mg of ridogrel in 80 ml of rectal solution can be prepared according to the above described preparation.

Clinical example

Three groups of patients suffering from mild to severe ulcerative colitis were treated orally for eight weeks with 5 mg ridogrel o.d. (group 1), 25 mg ridogrel b.i.d. (group 2) and 150 mg ridogrel b.i.d. (group 3).

The following findings were recorded:

	Group 1 (5 mg/day)	Group 2 (50 mg/day)	Group 3 (300 mg/day)
1. *Primary parameters*			
Endoscopic improvement	55%	46%	42%
Complete endoscopic cure	36%	17%	8%
2. *Secondary parameters*			
Median percentage of days with bloody stools during the last 2 weeks of treatment	0%	43%	92%
Percentage of patients wherein the investigator's global evaluation of the effect of the treatment was good or excellent	64%	46%	25%
3. *Adverse events*			
Occurrence of adverse events	36%	38%	54%

Conclusion

Both the treatment with 5 mg ridogrel o.d. and 25 mg ridogrel b.i.d. show improved clinical efficacy when compared with the 150 mg ridogrel b.i.d. treatment. Also the occurrence of adverse events is significantly less with the 5 mg ridogrel o.d. and 25 mg ridogrel b.i.d. treatment compared with the 150 mg ridogrel b.i.d. treatment.

Both the 5 mg ridogrel o.d. and 25 mg ridogrel b.i.d. treatment meet the definitions of a satisfactory treatment of ulcerative colitis as set forth hereinbefore.

Claims

1. The use of ridogrel for the manufacture of a medicament for treating inflammatory bowel diseases, wherein ridogrel is administered in a daily dose from 0.01 mg/kg body weight to 1 mg/kg body weight.

2. The use according to claim 1 wherein the daily dose of ridogrel is from 0.02 mg/kg body weight to 0.1 mg/kg body weight.

3. The use according to claim 1 wherein ridogrel is administered orally or rectally.

4. The use according to claim 1 wherein ridogrel is administered in combination with sulphasalazine, mesalazine or a corticosteroid.

5. The use of ridogrel for the manufacture of a medicament for treating inflammatory bowel diseases in adult human beings, wherein ridogrel is administered in a dose from 1 mg/day to 50 mg/day.

6. A pharmaceutical composition comprising from 0.5 to 10 mg ridogrel per dosage unit form and a pharmaceutically acceptable carrier.

7. A solid pharmaceutical composition comprising from 0.5 to 10 mg ridogrel per dosage unit form and a pharmaceutically acceptable carrier .

8. A solid pharmaceutical composition according to claim 7 consisting essentially of

ridogrel	1 mg	1.00 %
Calcium hydrogen phosphate dihydrate	0.94 mg	0.94 %
Lactose monohydrate	56.01 mg	56.01 %
Maize starch	24 mg	24.00 %
Croscarmellose sodium	2 mg	2.00 %
Sodium lauryl sulphate	0.25 mg	0.25 %
Hypromellose 2910 15 mPa.s	2 mg	2.00 %
Microcrystalline cellulose	10 mg	10.00 %
Croscarmellose sodium	3 mg	3.00%
Colloidal anhydrous silica	0.3 mg	0.30 %
Magnesium stearate	0.5 mg	0.50 %

9. A liquid pharmaceutical composition comprising from 0.1 to 1 mg/ml ridogrel and a pharmaceutically acceptable carrier .

10. A process for preparing a composition as claimed in claim 6 characterized in that ridogrel is intimately mixed with the pharmaceutically acceptable carriers.